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Original Article

Utility of a blood culture time to positivity-incorporated scoring model in predicting vascular infections in adults with nontyphoid *Salmonella* bacteremia

Jr-Jiun Lin [a], Tzu-Hua Weng [a], Wen-Pin Tseng [a], Shang-Yu Chen [a], Chia-Ming Fu [a], Hui-Wen Lin [b], Chun-Hsing Liao [b], Tai-Fen Lee [c], Po-Ren Hsueh [d], Shey-Ying Chen [a,*]

[a] *Department of Emergency Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*
[b] *Department of Internal Medicine, Far Eastern Memorial Hospital, Taipei, Taiwan*
[c] *Department of Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan*
[d] *Department of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*

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Abstract *Background:* Vascular infections (VI) are potentially catastrophic complications of nontyphoid *Salmonella* (NTS). We aimed to develop a scoring model incorporating information from blood culture time to positivity (TTP-NTSVI) and compared the prediction capability for VI among adults with NTS bacteremia between TTP-NTSVI and a previously published score (Chen-NTSVI).

Methods: This retrospective cohort study enrolled 217 adults with NTS bacteremia ≧ 50 years old. We developed a TTP-NTSVI score by multiple logistic regression modeling to identify independent predictors for imaging-confirmed VI and assigned a point value weighting by the corresponding natural logarithm of the odds ratio for each model predictor. Chen-NTSVI score includes hypertension, male sex, serogroup C1, coronary arterial disease (CAD) as positive predictors, and malignancy and immunosuppressive therapy as negative predictors. The prediction capability of the two scores was compared by area under the receiver operating characteristic curve (AUC).

* Corresponding author. Department of Emergency Medicine, National Taiwan University Hospital, College of Medicine, National Taiwan University, No 7 Chung-Shan South Road, Taipei, Taiwan.
E-mail address: erdrcsy@ntu.edu.tw (S.-Y. Chen).

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Results: The mean age was 68.3 ± 11.2 years-old. Serogroup D was the predominant isolate (155/217, 71.4%). Seventeen (7.8%) patients had VI. Four independent predictors for VI were identified: male sex (24.9 [2.59−239.60]; 6) (odds ratio [95% confidence interval]; assigned score point), peripheral arterial occlusive disease (9.41 [2.21−40.02]; 4), CAD (4.0 [1.16−13.86]; 3), and TTP <10 h (4.67 [1.42−15.39]; 3). Youden's index showed best cutoff value of ≧7 with 70.6% sensitivity and 82.5% specificity. TTP-NTSVI score had higher AUC than Chen-NTSVI (0.851 vs 0.741, $P = 0.039$).
Conclusion: While the previously reported scoring model performed well, a TTP-incorporated scoring model was associated with improved capability in predicting NTSVI.

Introduction

Non-typhoid salmonellae (NTS) are vital foodborne pathogens and cause a broad spectrum of human diseases ranging from self-limited gastroenteritis, primary bacteremia to life-threatening extra-intestinal complications including vascular or necrotizing soft tissue infection.[1−4] Among various extra-intestinal manifestations, vascular infection is especially challenging for first-line clinicians because of the difficulty in early detection and the narrow intervention window before rupture of infected aorta.[1,5−7] The overall mortality rate for NTS vascular infections was over 90% for patients with just medical treatment and approximately 40% for those with combined surgical and medical therapies.[5,6] Due to the high mortality risk from NTS-associated vascular complications, earlier diagnosis and prompt surgical intervention are crucial for the best treatment outcome for patients with NTS vascular infection.

Confirmation of endovascular infection relies on computed tomography (CT) or magnetic resonance (MR) imaging.[8,9] Because of the high prevalence of vascular infection among elderly patients with NTS bacteremia, it was suggested that patients > 50 years old with NTS bacteremia should undergo surveillance imaging tests, including CT to exclude the probability of concurrent endovascular infections.[10−14] However, evidence regarding universal surveillance imaging for all NTS bacteremia patients aged >50 years old to exclude the diagnosis of vascular infection remains inconclusive. This is an especially serious concern for communities with lower NTS vascular infection prevalence or limited medical resources. A decision rule that will facilitate risk stratification of vascular infection is therefore helpful for the timely and cost effective treatment of patients with NTS bacteremia. Chen and colleagues proposed a scoring model with the aim to predict the occurrence of NTS-related vascular infection (Chen-NTSVI score).[6] The Chen-NTSVI score identified hypertension, male sex, serogroup C1 NTS, and coronary artery disease (CAD) as positive predictors, and malignancy and immunosuppressive therapy as negative predictors for NTS-related vascular infection (Table 1). While the Chen-NTSVI score showed high sensitivity (95.0%) with an acceptable specificity (45.3%) at the cut-off value of +1, this model has never been validated independently. Furthermore, decline of serogroup C, particularly of the *Salmonella enterica serovar Choleraesuis* isolate, has been observed in Taiwan, possibly due to strict antibiotic usage regulation and the adoption of vaccination policies in hog farms.[15] The different microbiology pattern in NTS bacteremia between different communities may challenge the usefulness of a scoring model using a specific bacterial species as a model predictor.

Blood culture time to positivity (TTP) of a detected microorganism is defined as the time elapsed from inoculation to the detection of bacterial growth in a culture flask. Because TTP presumably reflects the bacterial inoculum size from cultured blood, it represents a quantitative surrogate parameter of bacteremia severity.[16,17] A previous study suggested that shorter TTP is associated with a higher likelihood of the presence of endovascular infection

Table 1 Independent predictors of Nontyphoid *Salmonella* Vascular Infection Score developed by Chen's research group (Chen-NTSVI Score).[6]

Risk factor	[a]OR (95% CI)	*P* value	Chen-NTSVI score	
			Model 1	Model 2
Hypertension	6.09 (2.93−12.66)	<0.0001	+6	+1
Male sex	4.13 (1.95−8.72)	<0.0001	+4	+1
Serogroup C1	4.03 (1.91−8.51)	<0.0001	+4	+1
Coronary arterial disease	2.50 (1.14−5.49)	0.02	+3	+1
Malignancy	0.38 (0.15−1.00)	0.05	−3	−1
Immunosuppressive therapy	0.20 (0.05−0.90)	0.04	−5	−1

[a] OR = adjusted odds ratio; CI = confidence interval.

sources and metastatic infection in *Staphylococcus aureus* bacteremia.[18] Because NTS shares similar tendency for endovascular complications to *S. aureus* bacteremia, we hypothesised that shorter TTP in NTS bacteremia may also be a useful predictor and may be incorporated into a scoring model for the prediction of NTS-related vascular infection. Therefore, the primary objective of this study was to develop a TTP-incorporated clinical scoring model to identify patients with NTS bacteremia at risk of vascular infection (TTP-NTSVI score). The secondary objective of this study was to compare the ability between TTP-NTSVI and Chen-NTSVI scores in predicting vascular infection in NTS bacteremia adult patients.

Methods

Patients, hospital setting and TTP measurement

We conducted this retrospective cohort study in the National Taiwan University Hospital, a 2500-bed medical center providing primary and tertiary care in northern Taiwan. All patients with blood cultures that yielded non-typhoidal *Salmonella* species between January 2013 and December 2016 were initially enrolled. Only the first episode was included regarding patients hospitalized for multiple incidents of NTS *Salmonella* bacteremia of the same serogroup. We excluded patients who were <50 years old, had polymicrobial bacteremia, or were not admitted to the study hospital. Data on demographic characteristics, comorbid medical conditions, imaging studies and treatment course during hospitalization, discharge diagnosis, and outpatient follow-up status were collected through electronic medical record review.

Blood cultures were obtained by inoculation of blood samples into aerobic and anaerobic blood culture flasks. Blood samples were incubated in a BACTEC FX blood culture system (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA) at the central microbiology laboratory, and monitored for carbon dioxide production signal every 10 min. The time from blood culture inoculation to the detection of positive fluorescent signal was routinely reported as TTP. In patients with multiple sets of positive blood cultures, the shortest TTP was used for analysis. All culture-positive blood samples were subcultured to identify bacterial isolates, according to the VITEK 2 automated microbiology system with conventional biochemical methods. Serogroups of *Salmonella* isolates were examined with O antiserum by slide agglutination. Antibiotics susceptibilities were evaluated via minimal inhibitory concentration determined with VITEK 2, according to Clinical Laboratory Standard Institute (CLSI) criteria.[19]

Information on variables and diagnosis of vascular infection

Several comorbid medical conditions were investigated. Malignancy included either an active malignant solid tumour or haematological disease. Chronic lung diseases included chronic obstructive pulmonary disease and asthma. Thrombocytopenia was defined as peripheral blood platelet count $<100{,}000/mm^3$. Immunosuppressive therapy included administration of corticosteroids, immunosuppressive agents, or chemotherapy within two weeks before the onset of NTS bacteremia.[6] The diagnosis of infection focus was based on clinical, laboratory, imaging, and associated microbiological investigations. Enteritis was defined as the presence of diarrheal symptoms and no other localizing focus, with or without a positive stool culture. Intra-abdominal infection was defined as localized infection of visceral organs, excluding enteritis. Diagnosis of vascular infection was based on the imaging findings (saccular or fusiform aneurysm, adjacent mass, irregular arterial wall with perifocal stranding, and/or fluid over the aorta or its branches) or pathology report of a surgical specimen.[6,8,9] Primary bacteremia was diagnosed in the absence of diarrheal symptoms and of detectable infection focus, during hospital discharge after extensive sepsis work-up.

Statistical analysis

Mean values (±SD) were calculated for continuous variables and percentages were used for categorical variables. An independent Student's *t*-test was used to compare continuous variables. The categorical variables were analysed with the Chi-squared method or Fisher exact test. Potential predictors for vascular infection with $P < 0.2$ on univariate analysis were investigated by multivariate logistic regression analysis, using a backward selection method.[20,21] The collinearity of the covariates was assessed and model fitting was explored based on the Hosmer–Lemeshow goodness-of-fit test. The discriminatory ability of each model was assessed by the area under the receiver operating characteristic (ROC) curve (AUC).[22]

To compare TTP-NTSVI with the published point-based Chen-NTSVI Score, we assigned a point value to each independent predictor selected by the final logistic regression model by multiplying the value of the corresponding natural logarithm (β-coefficient) of the odds ratio by 2 and rounding to the nearest integer (TTP-NTSVI Score Model 1).[23] We then modified the TTP-NTSVI Score Model 1 to a simpler model (TTP-NTSVI Score Model 2) constructed with equal weights for all related predictive variables of NTSVI. The overall score of each TTP-NTSVI Score model was the sum of the individual point values for each predictor. Sensitivity, specificity, positive predictive value, and negative predictive value with an associated 95% confidence interval (CI) for the prediction model at different cut-off values, were evaluated using standard definition and methods.[24] The best cut-off value for risk stratification of vascular infection of the final model was determined based on the Youden index statistics. Finally, AUC between the corresponding models of Chen-NTSVI and TTP-NTSVI Score were compared using the nonparametric approach.[25] Data were analysed with SPSS software for Windows (Version 22.0; IBM SPSS, Armonk, NY, USA). All *P* values are two-sided, and a *P*-value of <0.05 was considered statistically significant.

Results

A total of 217 adult patients with NTS bacteremia aged ≧50 years were enrolled in this study. Of those, 121 were male (55.8%). Mean age was 68.3 ± 11.2 years (range, 51–96). Serogroup D was the predominant isolate (155/217, 71.4%),

followed by serogroup B (18.4%) and C (6.9%). Malignancy was the most prevalent comorbid medical condition (50.2%), followed by hypertension (43.3%), diabetes mellitus (26.7%), CAD (15.2%) and liver cirrhosis (13.8%). A total of 61 (28.1%) patients received immunosuppressive therapy within 2 weeks prior to index blood culture. Overall TTP was 16.9 ± 14.6 h (range, 3.1–126.6 h). Univariate analysis showed that TTP <10 h (39/217, 18.0%) had the highest odds ratio [OR] for vascular infection (cut-off value, 8; OR, 0.719 ($P = 0.756$); cut-off value, 9; OR, 1.827 ($P = 0.373$); cut-off value, 10; OR, 3.675 ($P = 0.014$); cut-off value, 11; OR, 1.714 ($P = 0.297$); cut-off value, 12; OR, 1.375 ($P = 0.529$)). A total of 114 patients (52.5%) had undergone either CT (110 patients) or MR imaging (4 patients). Seventeen (7.8%) NTS patients were diagnosed with vascular infection during hospital discharge. Other bacteremia diagnoses included primary bacteremia (103 patients, 47.5%), enteritis-associated bacteremia (40 patients, 18.4%), intra-abdominal focus (19 patients, 8.8%), other infection focus (22 patients, 10.1%) and undetermined primary focus due to rapidly fatal course (16 patients, 7.4%).

Univariate comparisons of clinical characteristics and isolate serogroup distribution between NTS bacteremia patients with and without vascular infection diagnosis demonstrated a significantly higher percentage of male sex (94.1% vs 52.5%, $P = 0.001$), CAD (35.3% vs 13.5%. $P = 0.028$), peripheral arterial occlusive disease (PAOD) (29.4% vs 4.5%, $P = 0.002$), TTP < 10 h (41.2% vs 16.0%, $P = 0.017$) and lower percentage of malignant disease (23.5% vs 52.5%, $P = 0.022$) in the vascular infection group (Table 2).

Results of univariate and multivariate logistic regression analysis are shown in Table 3. The multivariate logistic regression model, which incorporated all potential predictors from univariate analysis, identified four independent predictors for NTS vascular infection: male sex (adjusted OR (aOR), 24.90; 95% CI, 2.59–239.60; $P = 0.005$), CAD (aOR, 4.00; 95% CI, 1.16–13.86; $P = 0.029$), PAOD (aOR, 9.41; 95% CI, 2.21–40.02; $P = 0.002$), and TTP < 10 h (aOR, 4.67; 95% CI, 1.42–15.39; $P = 0.011$). The Hosmer–Lemeshow goodness-of-fit statistic was 0.77. Table 3 shows the point values assigned to each predictor within models 1 and 2. Table 4 shows a complete summary of the diagnostic accuracy of the TTP-NTSVI Score models for various score cut-off values. The Youden index indicated that the TTP-NTSVI Score Model 1 performed best at a cut-off value of ≥7 points and the TTP-NTSVI Score Model 2 performed best at a cut-off value of ≥2 points. The prevalence of vascular infection among the 217 NTS bacteremia patients with low and high risk was 2.9% (5/170) and 25.5% (12/47) in TTP-NTSVI Score Model 1 and 3.0% (5/167) and 24.0% (12/50) in TTP-NTSVI Score Model 2, respectively.

Comparison of the AUCs between TTP-NTSVI and Chen-NTSVI Scores showed that both TTP-NTSVI Models 1 (0.851 vs 0.741, $P = 0.039$) and 2 (0.831 vs 0.748, $P = 0.181$) had higher AUC than Chen-NTSVI (Fig. 1).

Table 2 Univariate analysis of clinical characteristics in 217 adult patients with nontyphoid *Salmonella* bacteremia with or without vascular infection.

Characteristic	Vascular infection (n = 17)	No Vascular infection (n = 200)	*P*
Mean age ± SD (year)	70.4 ± 9.6	68.1 ± 11.4	0.226
Male sex	16 (94.1)	105 (52.5)	0.001
Comorbid medical condition			
Diabetes mellitus	7 (41.2)	51 (25.5)	0.164
Malignancy[a]	4 (23.5)	105 (52.5)	0.022
Liver cirrhosis	2 (11.8)	28 (14.0)	1.000
End stage renal disease	1 (5.9)	10 (5.0)	0.601
Chronic lung disease	2 (11.8)	13 (6.5)	0.332
Hypertension	10 (58.8)	84 (42.0)	0.179
Congestive heart failure	4 (23.5)	26 (13.0)	0.265
Coronary arterial disease	6 (35.3)	27 (13.5)	0.028
Ischemic stroke	1 (5.9)	16 (8.0)	1.000
PAOD	5 (29.4)	9 (4.5)	0.002
HIV infection	0 (0)	5 (2.5)	1.000
Immunosuppressive therapy	3 (17.6)	58 (29.0)	0.408
Thrombocytopenia	5 (29.4)	59 (29.5)	0.994
Serogroup B Infection	3 (17.6)	37 (18.5)	1.000
Serogroup C Infection	0 (0)	15 (7.5)	0.614
Serogroup D infection	13 (76.5)	142 (71.0)	0.783
TTP <10 h	7 (41.2)	32 (16.0)	0.017

PAOD = peripheral arterial occlusive disease; HIV = human immunodeficiency virus; TTP = time to positivity.
[a] Includes haematological and solid organ malignancy.

Discussion

In the current study, we developed a new score-based prediction model incorporating information from blood culture TTP. We compared our model to a published scoring model to evaluate the capability of risk stratification of vascular infection among adult patients with NTS bacteremia. We found that epidemiology, microbiology and clinical characteristics of adult patients with NTS bacteremia in Taiwan were rapidly changing in recent decades. The prevalence of vascular infection among adult patients with NTS bacteremia declined. We proved that blood culture TTP was independently associated with the risk of NTS-related vascular infection. Finally, although the Chen-NTSVI scoring model was useful in predicting vascular infection among NTS bacteremia patients, a model utilizing TTP and additional factors based on modern epidemiology was associated with improved performance.

The need to stratify patients at risk of vascular infection is particularly relevant to those with bloodstream infections caused by nontyphoidal *Salmonella*. Early diagnosis of vascular infection for timely surgical intervention before aneurysmal rupture is crucial to improve clinical outcomes of patients with NTS bacteremia.[5,6] The diagnosis of vascular infection is straightforward when CT or MRI shows characteristic imaging findings in patients with documented NTS bacteremia. The challenge in the management of NTS bacteremia in adults is therefore the decision of selecting patients for contrast-enhanced CT examination to avoid unnecessary contrast median and radiation exposure for patients with low risk of vascular infection. In our study, we demonstrated that the proposed TTP-NTSVI score, at a cut-off value ≧6 in model 1, could effectively stratify low and high vascular infection risk and significantly reduce the need for CT examination (128/217,

Table 3 Logistic regression analysis for independent factors associated with vascular infection and the development of time to positivity-incorporated nontyphoid *Salmonella* vascular infection score (TTP-NTSVI Score).

Risk factor	Univariate	Multivariate			TTP-NTSVI score	
	Odds ratio (95% CI)	Odds ratio (95% CI)	β	*P* value	Model 1	Model 2
Male sex	14.48 (1.88–111.25)[a]	24.90 (2.59–239.60)[b]	3.21	0.005	6	1
Community onset	0.96 (0.26–3.51)	–	–	–	–	–
Diabetes mellitus	2.05 (0.74–5.65)	–	–	–	–	–
Hypertension	1.97 (0.72–5.39)	–	–	–	–	–
Malignancy	0.28 (0.09–0.88)[a]	–	–	–	–	–
Liver cirrhosis	0.82 (0.18–3.78)	–	–	–	–	–
Coronary artery disease	3.50 (1.19–10.23)[a]	4.00 (1.16–13.86)[a]	1.39	0.029	3	1
Congestive heart failure	2.06 (0.62–6.80)	–	–	–	–	–
Cerebral vascular disease	0.72 (0.09–5.78)	–	–	–	–	–
PAOD	8.84 (2.56–30.53)[b]	9.41 (2.21–40.02)[b]	2.24	0.002	4	1
Thrombocytopenia	1.00 (0.34–2.95)	–	–	–	–	–
Immunosuppressant	0.53 (0.15–1.89)	–	–	–	–	–
Serogroup D infection	1.33 (0.42–4.24)	–	–	–	–	–
TTP < 10 h	3.68 (1.30–10.37)[a]	4.67 (1.42–15.39)[a]	1.54	0.011	3	1

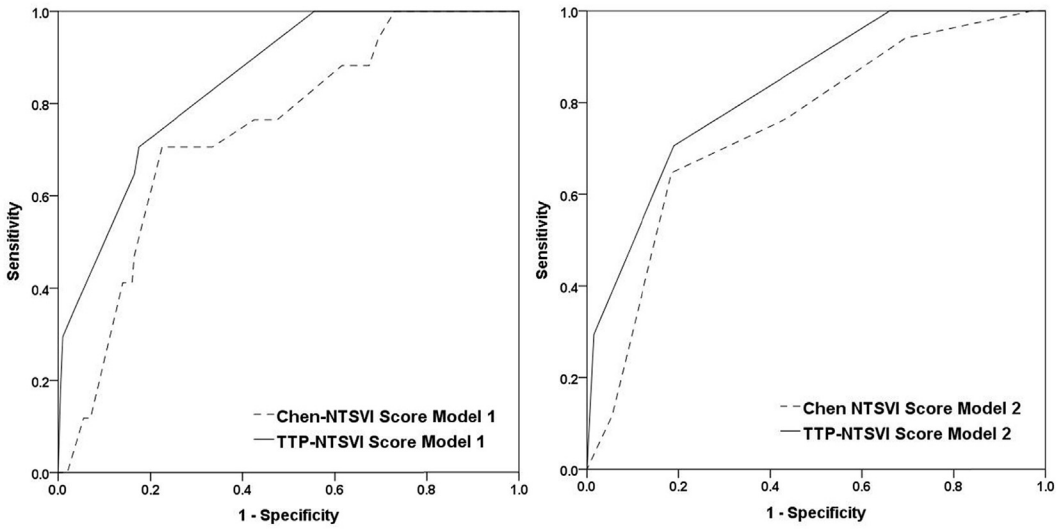
PAOD = peripheral arterial occlusive disease; TTP = time to positivity.
[a] $P < 0.05$.
[b] $P < 0.01$.

59.0%) with high detection sensitivity (100%; 95% CI, 81.6–100%) and negative prediction value (100%; 95% CI, 95.9–100%). If the best cut-off value ≧7 in model 1 was adopted, as determined by the Youden index, the TTP-NTSVI score could further reduce the need for CT examination (47/217, 21.7%) with satisfactory sensitivity (70.6%; 95% CI, 46.9–86.7%) and high negative prediction value (97.1%; 95% CI, 93.3–98.7%). Therefore, we would recommend CT examination for all NTS bacteremia adults aged ≧ 50 years with a TTP-NTSVI Score Model 1 of ≧7. For those with a score of 6, surveillance chest roentgenogram and abdominal sonography may be considered before the decision of CT imaging.[26]

There were significant differences in patient characteristics, microbiology, and prevalence of vascular infection between our study and the previous study reporting the Chen-NTSVI score. Higher prevalence of *Salmonella* serogroup C (18.2% vs 6.9%, $P < 0.001$) and chronic lung disease (13.1% vs 6.9%, $P = 0.020$) and lower prevalence of malignancy (33.5% vs 50.2%, $P < 0.001$) and receiving immunosuppressive therapy (17.0% vs 28.1%, $P = 0.002$) among patients were observed in Chen's study compared to our study. The occurrence of vascular infection was positively associated with *Salmonella* C1 serogroup isolates, whereas it was negatively associated with malignancy and receiving immunosuppressive therapy.[6,10,11] Therefore, different microbiology and patient characteristics may account for the disparate prevalence of vascular infection in NTS bacteremia patients between the two studies. Decline of vascular infection prevalence in adult NTS bacteremia patients in Taiwan was supported by different

Table 4 Accuracy of the risk score in the identification of concurrent vascular infection among 217 nontyphoid *Salmonella* bacteremia patients, stratified according to the cutoff value of the risk score.

Cutoff value	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive predictive value, % (95% CI)	Negative predictive value, % (95% CI)	Number of cases (% of entire cohort)	Youden index
TTP-NTSVI Model 1						
≥13	17.6 (6.2–41.0)	99.5 (97.2–99.9)	75.0 (30.1–95.4)	93.4 (89.3–96.0)	4 (1.8)	0.17
≥12	29.4 (13.3–53.1)	99.0 (96.4–99.7)	71.4 (35.9–91.8)	94.3 (90.3–96.7)	7 (3.2)	0.28
≥10	35.3 (17.3–58.7)	96.5 (93.0–98.3)	46.2 (23.2–70.9)	94.6 (90.6–97.0)	13 (6.0)	0.32
≥9	64.7 (41.3–82.7)	83.5 (77.7–88.0)	25.0 (14.6–39.4)	96.5 (92.6–98.4)	44 (20.3)	0.48
≥7	70.6 (46.9–86.7)	82.5 (76.6–87.1)	25.5 (15.3–39.5)	97.1 (93.3–98.7)	47 (21.7)	0.53
≥6	100.0 (81.6–100.0)	44.5 (37.8–51.4)	13.3 (8.5–20.2)	100.0 (95.9–100.0)	128 (59.0)	0.45
≥4	100.0 (81.6–100.0)	44.0 (37.3–50.9)	13.2 (8.4–20.1)	100.0 (95.8–100.0)	129 (53.3)	0.44
≥3	100.0 (81.6–100.0)	34.0 (27.8–40.8)	11.4 (7.3–17.5)	100.0 (94.7–100.0)	149 (68.7)	0.34
≥0	100.0 (81.6–100.0)	0.0 (0.0–1.9)	7.8 (–)	–	217 (100.0)	0.0
TTP-NTSVI Model 2						
≥3	29.4 (13.3–53.1)	98.5 (95.7–99.5)	62.5 (30.6–86.3)	94.3 (90.2–96.7)	8 (3.7)	0.28
≥2	70.6 (46.9–86.7)	81.0 (75.0–85.8)	24.0 (14.3–37.4)	97.0 (93.2–98.7)	50 (23.0)	0.52
≥1	100.0 (81.6–100.0)	34.0 (27.8–40.8)	11.4 (7.3–17.5)	100.0 (94.7–100.0)	149 (68.7)	0.34
≥0	100.0 (81.6–100.0)	0.0 (0.0–1.9)	7.8 (5.0–12.2)	–	217 (100.0)	0.0



	Model 1		Model 2	
	AUC	(95% CI)	AUC	(95% CI)
Chen-NTSVI Score	0.741	(0.629-0.852)	0.748	(0.630-0.866)
TTP-NTSVI Score	0.851	(0.769-0.932)	0.831	(0.737-0.925)

Figure 1. Receiver operating characteristic (ROC) curves and associated area under the ROC curve (AUC) for the Chen-NTSVI and TTP-NTSVI Scores.

studies, ranging from 21.5% (26/121) in an earlier study conducted between 1995-2001,[11]—16.8% (60/358) in Chen's study conducted between 1994-2009,[6]—9.1% (6/66) in Lin' s study conducted in 2010—2012,[17] and to 7.8% (17/217) in our study. More importantly, variations in the prevalence of malignancy, receiving immunosuppressant therapy and *Salmonella* serogroup C1 rendered the previously useful Chen-NTSVI score less effective for the prediction of NTS-related vascular infection in modern era. A new prediction model utilizing factors based on modern epidemiology, as proposed in this study, is therefore required for improved performance.

Blood culture TTP is a newly-developed laboratory index. Based on the estimation of the initial bacterial inoculum in cultured blood, it was proved to be a useful surrogate indicator of the severity of bacteremic infection and independently predicted clinical outcomes for patients with *S. aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* bacteremia.[18,27—33] However, prior to this study, the association of shorter TTP with higher risk of endovascular and metastatic infection was observed only in patients with *S. aureus* bacteremia. In our study, we demonstrated that TTP was an independent predictor for vascular infection in patients with NTS bacteremia. Our study therefore supports the idea that TTP is useful for providing both prognostic and diagnostic information for first-line physicians in treating patients with bloodstream infections. In addition, we demonstrated that TTP could be integrated in and improve a prediction model regarding risk stratification of vascular infection in NTS bacteremia patients.

There are limitations in this study. First, clinical data of study patients in this observational cohort were retrospectively collected. This inevitably introduced information bias. Second, because only 52.5% (104/217) of our NTS bacteremia patients underwent either CT or MR imaging during index hospitalization, the true incidence of vascular infection may have been underestimated and may have introduced a classification bias in this study. However, because 80% of 164 patients, who survived to index hospitalization discharge, were regularly followed up in our outpatient clinics and none of the 12 patients with recurrent bacteremia after index hospitalization discharge had subsequent diagnosis of vascular infection, the probability of underdiagnosis was low in our study. Third, being a non-protocolled study, the volume of blood drawn for culture was not recorded. However, we assumed that such variations were randomly distributed and did not affect our results. Last, the generalizability of TTP-NTSVI score has not been validated independently.

In conclusion, there are significant changes in microbiology, clinical characteristics and prevalence of vascular infection in adult patients with NTS bacteremia in modern era. Therefore, a previous excellent scoring model may be unable to properly predict the possibility of vascular infection in adults with NTS bacteremia. A new TTP-NTSVI score utilizing independent predictors including blood culture TTP $<$10 h, male sex, coronary artery disease, and peripheral arterial occlusive disease based on modern epidemiology was associated with improved performance in the prediction of vascular infection among patients with NTS bacteremia.

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Conflicts of interest

The authors declare no conflicts of interest in relation to this study.

Ethical approval

The study was approved by the Research Ethics Committee in National Taiwan University Hospital (201410071RINB).

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